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10/720,662

11/24/2003

Hong-Mo Moon

038779/271509

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01/11/2005

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EXAMINER

LUCAS, ZACHARIAH

ART UNIT

PAPER NUMBER

1648

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/720,662

Applicant(s)

MOON ET AL.

Examiner

Zachariah Lucas

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-43 is/are pending in the application.
- 4a) Of the above claim(s) 1-5, 13 and 19-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6-12 and 14-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11-24-03, 6-28-04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Currently, claims 1-43 are pending in the application. In the restriction requirement mailed on October 6, 2004, a requirement for restriction was made between claims 6-13 (Group II) and claims 14-19 (Group III) on the grounds that the claims were being read as though the term "transformant" included transgenic animals. However, upon further review of the application, it is noted that only transformants specifically identified by the application are transformed yeast cells. See e.g., pages 11-12. The application does not anywhere indicate that transgenic animals were contemplated as part of the claimed invention. In view of this, the application is deemed not to cover such embodiments. The requirement for restriction is therefore withdrawn to the extent that the claims of Groups II and III are identified as separate groups. Thus, claims 6-19 are now considered to be part of the same Group of inventions.

2. Claims 1-5, 13, and 19-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 4, 2004.

Claims 13 and 19 are withdrawn as to non-elected species of the claimed inventions. This is because these inventions are drawn to compositions comprising unmodified versions of the pre-S sequences.

3. Applicant's election without traverse of Group III, and the inventions represented by the election of the adr subtype, modifications at both positions 15 and 123 of the HBV pre-S

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sequence, and to embodiments wherein the asparagines at these positions are replaced by histidines in the reply filed on November 4, 2004 is acknowledged.

In view of the withdrawal of the restriction between Groups II and III, claims 6-12 and 14-18 are currently under consideration to the extent that they read on, or are generic to, the elected inventions.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on November 24, 2003, and on June 28, 2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 6-12 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Kniskern et al. (U.S. Patent 5,614,384) in view of Takahashi et al. (Arch Virol 143: 2313-26) and of Essex (U.S. Patent 6103, 238) and O.Narhi et al. (Protein Engineering 14: 135-40). These claims are directed to mutated HBV pre-S genes (and vectors or transformants thereof) wherein the gene has been mutated such that the expressed pre-S protein is not glycosylated. In particular, the claims are directed to mutated forms of the pre-S genes of HBV

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wherein the asparagines at positions 15 and 123 have each been substituted with a histidine such that the residues at those positions are not glycosylated.

Kniskern teaches methods of producing non-N-glycosylated versions of the S antigens of HBV. The reference indicates that such versions of the proteins, especially when recombinantly produced in yeast cells, are preferable because they reduce the chance of the generation of anti-yeast antibodies, or of the antigens being bound by anti-yeast antibodies already in an animal to be immunized. Column 3, lines 33-60. The reference teaches that such versions of the HBV antigens result in a more effective anti-HBV immunogenic compositions. Id. While the reference is primarily concerned with achieving the reduced glycosylation through use of particular cells (claim 1), the reference also teaches that an alternative means of achieving this goal is through modification of the glycosylation recognition site. Column 4, lines 6-13. Kniskern teaches that the recognition sites of N-glycosylation comprise the sequences Asn-X-Ser or Asn-X-Thr, wherein the X may be any amino acid. Column 3 lines 7-15. Finally, the reference teaches that these teachings may be applied against any of the S-antigens, including the pre-S1 antigen. Column 3, lines 26-31. However, the reference does not specifically indicate that the asparagine may be substituted with histidine, or provide the specific HBV sequences that may be substituted.

Takahashi teaches the full-length sequences of several Hepatitis B virus isolates. Because the teachings of Kniskern refer to the modification of HBV sequences in general, it would have been apparent that the modifications may be made to the sequence of any isolate of HBV. Takahashi teaches the sequences of two isolates (represented by Protein Database accession numbers BAA32887 and BAA32860) that match the sequences provided in the present

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application for adr type genotypes (SEQ ID NO: 4, and SEQ ID NO: 11- which varies from SEQ ID NO: 4 at position 60, as well as by including the Asn→His substitutions). Examination of either of these sequences for the N-glycosylation recognition sites shows that the only N-glycosylation sites in the pre-S sequence are those corresponding to residues 15 and 123. Thus, from the teachings of Kniskern and Takahashi, it would have been obvious to those in art to have substituted another amino acid for the asparagine residues of positions 15 and 123.

It is also noted that Kniskern does not teach that the asparagines may be substituted with histidines. However, the teachings of Kniskern indicate that any substitution may be made so long as the recognition sequence is removed. The teachings of O.Narhi, which relate to the modification of EPO such that N-glycosylation does not occur, indicates that additional benefits may be found in the form of additional stability where basic amino acids, which would include lysine and histidine, are substituted for the asparagine. Additionally, the teachings of Essex indicate that substitution of an asparagine for a histidine in an Asn-X-Ser/Thr site results in a lack of N-glycosylation at that site. See e.g., columns 6-7. From these teachings, it would have been obvious to those in the art that any amino acid, including histidine, may be substituted for asparagine to prevent N-glycosylation.

From the combined teachings of the references, it would therefore have been obvious to those in the art that the HBV pre-S sequence may be modified as suggested by Kniskern through the substitution of asparagine for histidine so as to prevent glycosylation of the proteins when expressed in yeast cells. The additional teaching of Takahashi would have rendered obvious the specific sequences of present application. Those of skill in the art would have had a reasonable expectation of success in such modifications based on the teachings of Kniskern, and based on

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the teachings of O.Narhi and other references (e.g. Marini et al., Molec Microbiol 38: 552-64) demonstrating successful prevention of N-glycosylation in other proteins through substitution of asparagine in recognition sites with another amino acid.

7. Claims 6-12 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Comberbach et al. (U.S. Patent 6,103,519) in view of Takahashi and Essex. The claims have been described above.

Comberbach teaches vectors and cells transformed with recombinant molecules encoding the HBV pre-S antigen. Columns 22-23. The reference additionally teaches that the disclosed HBV sequences include proteins modified by the elimination of potential glycosylation sites, including N-glycosylation sites. Column 19, lines 22-31; and column 20-21. In particular, the reference identifies N-glycosylation sites as those “characterized by the sequence Asn-X-(Ser or Thr). Id. The reference indicates that such elimination may be performed by “deleting or replacing” the asparagine or serine or threonine in the N-glycosylation site. The reference does not however teach that the asparagine may be substituted with a histidine or the specific sequence of SEQ ID NO: 11. However, additional teachings rendering these additional limitations obvious are provided in the Takahashi and Essex references as described above. The combined teachings of these references therefore render the claimed inventions obvious.

Conclusion

8. No claims are allowed.

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9. The following prior art references are made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

Okuda et al., U.S. Pub 2003/0165534. This reference provides teachings relevant to those of the presently claimed invention in that it teaches the modification of N-glycosylation sites in antigens expressed in transformants. However, the reference does not teach that the antigen is the pre-S protein of HBV, or the particular HBV sequences to be modified.

Petre et al., Postgrad Med J 63: 73-81. This reference teaches that yeast cells may be used to recombinantly produce HBV antigens for use in anti-HBV vaccines.

Shouval et al., Vaccine 12: 1021-25. This reference provides additional teachings indicating that inclusion of the pre-S domains in HBV vaccines improves the efficacy of HBV S-protein vaccines.

Biemans et al., DNA Cell Biol 10: 191-200. This reference teaches post-translation modification of HBV proteins expressed in yeast cells.

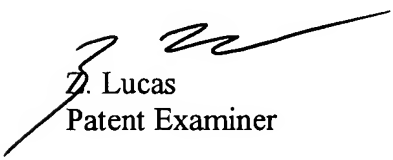
Kniskern et al., Vaccine 12:1021-25. This reference suggests the production of HBV particles in yeast cells deficient in their ability to glycosylate the proteins, and indicates that there are N-glycosylation sites in both the pre-S1 and pre-S2 regions of the HBV pre-S antigen. Page 1021, right column. The reference is considered redundant to the teachings of the Kniskern patent applied above.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



J. Lucas
Patent Examiner



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